

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

2-(2-(p-(DIISOBUTYL)PHENOXY)ETHOXY)ETHYL DIMETHYL BENZYL AMMONIUM  
CHLORIDE  
(HYAMINE 1622)

Chemical Code # 000066, DPN 50421

SB 950 # 443

Original date: September 10, 1987

Updated: June 22, 2004

I. DATA GAP STATUS

Combined, rat: (chronic & Onco)	Data gap, inadequate study, possible adverse effect indicated.
Chronic dog:	Data gap, inadequate study, no adverse effect indicated.
Onco rat:	See combined , rat.
Onco mouse:	Data gap, inadequate study, no adverse effects indicated.
Repro rat:	Data gap, no study on file.
Terato rat:	No data gap, no adverse effects indicated.
Terato rabbit:	Data gap, no study on file.
Gene mutation:	Data gap, inadequate study, no adverse effects indicated.
Chromosome:	Data gap, inadequate study, no adverse effects indicated.
DNA damage:	Data gap, inadequate study, no adverse effects indicated.
Neurotox:	Not required at this time.

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Note, Toxicology one-liners are attached.

\*\* indicates acceptable study

Boldface indicates possible adverse effect

File name: T040622

Update: Kishiyama and Gee, 6/22/04

This active ingredient has been grouped in 1998 by the US Environmental Protection Agency with other antimicrobial ADBAC compounds, as Case 350. The Department of Pesticide Regulation

has not made such a grouping. For those active ingredients that the Department has grouped, all data requirements under SB950 have been met - see DPN 50238, CC 1846.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### COMBINED, RAT

50421 - 019 144211 Lambright, D. D., J. R. Beverly, S. R. Gunnels, T. A. King-Hunter, T. L. Rhoades, and K. L. Shaw. "Toxicology and Carcinogenesis Studies of Benzethonium Chloride in F344/N Rats and B6C3F1 Mice (Dermal Studies)." (Battelle Columbus Laboratories, NTP TR 438, NIH Publication No. 94-3169, July, 1995). Benzethonium chloride, purity +98.5%, at doses of 0.15, 0.5, or 1.5 mg/kg in 95% ethanol, was administered topically to the skin (clipped of fur) of 60 F344/N rats/sex/group, 5 days/week for 2 years. A limited number of animals (4 to 9 per sex/dose) were evaluated after 15 months. A 16-Day and a 13-Week study (10/sex/dose) served as preliminary dose range-finding studies for the 2-year study. Details of the percent of body surface, length of exposure in hours per day and method of occlusion were not given. Dermal NOEL = 0.15 mg/kg/day: increased incidence of nonneoplastic lesions (epithelial hyperplasia, sebaceous gland hyperplasia, and ulceration) to the treated skin at 0.5 and 1.5 mg/kg with the incidences increasing with dose. No individual data for skin effects. Individual data for tumors only. No evidence of oncogenicity at the site of exposure. UNACCEPTABLE (lacks some parameters needed for a chronic toxicity study; as an oncogenicity study, the report contains insufficient information). (Kishiyama and Gee, 6/16/2004).

50421 016 135087 Draft report for 019 144211.

### CHRONIC TOXICITY, RAT

50421-002 38554 Finnegan, J. K. and J. B. Dienna "Toxicity of quaternaries." (Medical College of Virginia and Rohm and Haas, Publ. in *Soap and Sanitary Chemicals*, 2/1954, presented in 12/8/53). Hyamine 1622, in a diet mix at 0, 50, 200, 1000, 2500, and 5000 ppm, was fed to albino rats (10/sex/group) for 2 years. At 5000 ppm, half the animals had died by week 30. Adverse effects noted: decreased weight at 2500 (slight, late in the study) and 5000; 1/6 males at 2500 and 2/3 males at 5000 ppm had testicular atrophy at necropsy; apparent NOEL (chronic) = 1000 ppm. UNACCEPTABLE (no individual data, no dose analysis, no food consumption, insufficient number of animals, inadequate animal description); not upgradeable (Aldous, 6/5/85). Subsequent review (Harnois, 9/10/87) for clarification of test substance as SB443. Addition: Hyamine 2389 (alkyl (C9 to C15) tolyl methyl trimethyl ammonium chloride) was also included in the study with diets containing 0, 50, 200, 1000, 2500 and 5000 ppm with 10/sex/dose. Survival was lower at 5000 ppm with 0 survival by 30 weeks. Body weight was lower at 2500 ppm.. (Gee, 6/16/04)

### CHRONIC TOXICITY, DOG

50421-002 23487 Finnegan, J. K. and J. B. Dienna "Toxicity of quaternaries." (Medical College of Virginia and Rohm and Haas, Publ. in *Soap and Sanitary Chemicals*, 2/1954, presented in 12/8/53). Hyamine 1622 in diet mix at 5, 100, and 500 ppm was fed to dogs (unspecified mongrel, 3/group) for 1 year. No adverse effects reported. UNACCEPTABLE (Inadequate test description and reporting of data, multiple deficiencies). Not upgradeable. (Aldous, 6/5/85). Subsequent review confirmed identity of test substance as SB#443 (Harnois, 9/10/87)

### ONCOGENICITY, RAT

See combined, rat

### ONCOGENICITY, MOUSE

50421 - 019 144211 Lambright, D. D., J. R. Beverly, S. R. Gunnels, T. A. King-Hunter, T. L. Rhoades, and K. L. Shaw. "Toxicology and Carcinogenesis Studies of Benzethonium Chloride in F344/N Rats and B6C3F1 Mice (Dermal Studies)." (Battelle Columbus Laboratories, NTP TR 438, NIH Publication No. 95-3169, July 1995.) Benzethonium chloride, purity +98.5%, at doses of 0.15, 0.5, or 1.5 mg/kg in 95% ethanol, was administered topically to the skin (clipped of fur) of 60 B6C3F<sub>1</sub> mice/sex/group, 5 days/week for 104 weeks. A limited number were evaluated after 15 months. A 16-Day and 13-Week studies served as preliminary dose range-finding studies for the 2-Year study. Details of the percent body surface, length of exposure per day and method of occlusion were not given. Increased incidence of epithelial and sebaceous gland hyperplasia at the treatment site: Dermal NOEL = 0.15 and 0.5 mg/kg/day for males and females, respectively. No individual data for skin effects. Individual data for tumors only. No hematology, urinalysis or ophthalmology was performed. UNACCEPTABLE (oncogenicity study with insufficient information). Possibly upgradeable (individual dermal data, exposure details) (Kishiyama and Gee, 6/17/04).

50421 016 135087 Draft report for 144211.

### REPRODUCTION, RAT

No study submitted

### TERATOLOGY, RAT

50421 - 017 141541 Foss, J. A. A Dose Range-Finding Developmental Toxicity Study of Hyamine 7 1622 in Rats. (Argus Research Laboratories, Inc., Laboratory Project ID: Protocol Number 720-002P, October 3, 1995.) Benzethonium Chloride (Hyamine 7 1622), purity 99.3%, was administered via gavage at doses of 0 (water), 3, 10, 30, 100, or 150 mg/kg/day during gestation days 6 through 15 to 8 mated Sprague-Dawley female rats/group. The incidence of agnathia for high dose fetuses (2/7 litters = 28.6% compared with historical control incidence of range of 0 - 7.1%) was reported as not related to Hyamine 7 1622 treatment, based on no other alterations and the lack of agnathia in the definitive study, record 144210.

High dose rats had soft or liquid feces and slightly lower body weight, body weight change and food consumption. The author suggested 10, 30, 100 and 170 mg/kg doses for the main developmental study. Supplemental study. (Kishiyama and Gee, 6/20/04).

\*\* 018 144210 Foss, J. A. "Developmental Toxicity Study of Hyamine® 1622 in Rats." (Argus Research Laboratories, Inc., Laboratory Project ID: Protocol Number 720-002, October 26, 1995.) Benzethonium Chloride (Hyamine® 1622), purity 99.3%, was administered via gavage at doses of 0 (water), 10, 30, 100, or 170 mg/kg/day during gestation days 6 through 15 to 25 mated Sprague-Dawley female rats/group. Body weight and bodyweight change were lower for the high dose group and food consumption reduced. Clinical signs were noted at the high dose, including fecal changes (soft, no or liquid), salivation, and staining of fur. Four dams died (gestation days 11, 12, 13 or 16) at 170 mg/kg/day, considered related to treatment. Maternal NOEL = 100 mg/kg (clinical signs, mortality, lower body weight). Developmental NOEL = 170 mg/kg. ACCEPTABLE. (Kishiyama and Gee, 6/21/04).

#### TERATOLOGY, RABBIT

No study submitted

#### GENE MUTATION

019, 021 144211, 147803 Lambright, D. D., J. R. Beverly, S. R. Gunnels, T. A. King-Hunter, T. L. Rhoades, and K. L. Shaw. "Salmonella Mutagenicity Test Protocol." (Case Western Reserve University, NTP TR 438, NIH Publication No. 95-3169, 1995). Benzethonium chloride was evaluated for mutagenicity at concentrations ranging from 0 (distilled water) to 1 µg/plate without activation and 1 to 100 µg/plate, with metabolic activation (S9 Mix, 10% hamster S9 or 10% rat S9), using Salmonella typhimurium strains TA 1535, TA1537, TA98, and TA 100. The test material was incubated with the bacteria for 20 minutes before plating (preincubation method). Details of the S9 mix, volumes used and individual plate counts were not included. There were triplicate plates per concentration and two trials. No increase in revertants with benzethonium chloride treatments without or with metabolic activation. UNACCEPTABLE (insufficient information). Possibly upgradeable. Record 147803 contains additional data from a study conducted at SRI International with strains TA100 and TA1535 using (apparently) a similar protocol with preincubation and DMSO as the solvent. These results were also negative. (Kishiyama and Gee, 6/17/04).

#### CHROMOSOME EFFECTS

019, 021 144211, 147803 Lambright, D. D., J. R. Beverly, S. R. Gunnels, T. A. King-Hunter, T. L. Rhoades, and K. L. Shaw. "Chromosome Aberration Test." (Columbia University, NTP TR 438, NIH Publication No. 95-3169, 1995.) Benzethonium chloride (specific lot not given) was evaluated for chromosomal aberrations at concentrations of 0 (distilled water), 0.96, 3, and 9.6 µg/mL without metabolic activation and at 0 (distilled water), 3, 9.6, and 30 µg/mL with Aroclor 1254-induced rat liver S9 Mix using Chinese Hamster ovary cells. Without activation, cells were incubated for 12 hours plus 2 with colcemid before harvest. With activation, treatments lasted 2

hours followed by 12 hours of further incubation before harvest. The number of cultures per concentration is unclear but 100 cells were scored for aberrations per concentration. Chromosomal aberrations for benzethonium chloride treatments with and without S9 Mix were not statistically significant. Positive controls were functional. In record 147803, data from Litton Bionetics, 8/21/85, were presented for a single trial with and without activation at concentrations of 0 (negative and DMSO), 745, 801, and 14900 (insoluble)  $\mu\text{g/mL}$  without activation and at 0, 499, 700, 745 and 14900  $\mu\text{g/mL}$  with rat liver activation. One hundred cells were scored per concentration. No treatment-related increase in chromosomal aberrations was reported, although only the final data were presented with no details of study conduct. UNACCEPTABLE (major variances from guideline). (Kishiyama and Gee, 6/18/04).

### DNA DAMAGE

019, 021 147803, 144211 Lambright, D. D., J. R. Beverly, S. R. Gunnels, T. A. King-Hunter, T. L. Rhoades, and K. L. Shaw. "Chinese Hamster Ovary Cell Cytogenetics Protocols." (Columbia University, NTP TR 438, NIH Publication No. 95-3169, 1995.) Benzethonium chloride (lot not identified) was evaluated for mutagenicity at concentrations of 0 (distilled water), 0.96, 3, and 9.6  $\mu\text{g/mL}$  without metabolic activation and at 0 (distilled water), 3, 9.6, and 30  $\mu\text{g/mL}$  with Aroclor 1254-induced rat liver S9 Mix using Chinese Hamster ovary cells. Treatment without activation was for 26 hours and for 2 hours with activation followed by an additional 26 hours. BrdU was present. Cells were harvested by mitotic shake-off and stained. Fifty cells per from one flask were scored for sister chromatid exchanges. Positive controls were functional. Benzethonium chloride with or without metabolic activation did not significantly induce SCE's in Chinese hamster ovary cells. Additional data were submitted in record 147803 from Litton Bionetics, dated 8/21/85 in which benzethonium chloride was tested in two trials without activation. In trial 1, concentrations were 0 (DMSO), 17.9, 49.7, 149 and 497  $\mu\text{g/mL}$  with 50 cells scored per concentration. In trial 2, concentrations were 0, 499, 596, 700 and 801  $\mu\text{g/mL}$ . The highest concentration yielded no cells. Both assays were concluded to be negative for SCEs. The positive control, mitomycin C, was functional. UNACCEPTABLE (major variances from guideline for each laboratory). (Kishiyama and Gee, 6/18/04).

### NEUROTOXICITY

Not required at this time.